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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/747,798	12/29/2003	George H. Yoo	INRP:104US	1871

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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/747,798	YOO, GEORGE H.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040816*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The citations on the PTO-1449 of documents C1, C2, C23, C24, and C95 provided with the information disclosure statement filed 8/16/05 do not fully comply with 37 CFR 1.98(b)(c), which requires that non-patent documents be identified by date of publication, location of publication, etc. These documents have been reviewed, but their citations have been crossed out as not being suitable for printing on the face of a patent due to the omission of the required information. Applicant's attention is directed to the request for information under 37 CFR 1.105 regarding document C95 at the end of this Office action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-12, 15, 18, 23-28, 30, 33, 36, 38-48, 51, and 54 are rejected under 35 U.S.C. 102(a) as being anticipated by Clayman, G., Ref. C95 of the IDS filed 8/16/04, as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998), and as evidenced by Recombinant DNA Advisory Committee (RAC), Minutes of Meeting March 8, 2001, U.S. Dept. of health and Human Services.

Clayman describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector (see pages 4-6 especially).

Clayman does not mention papilloma virus infection of cells in the lesion, however, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment. Oda discloses that up to 90% of oral cancers have been reported to contain HPV DNA (p. 2003, col. 2), and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Consequently, one of skill in the art of oral cancer would have been

aware that the treatment of Clayman would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of target patients. With respect to the limitation that the composition be formulated as a douche solution (e.g. claims 18, 33, 54), a douche is simply a jet of liquid applied to a part of the body; so a douche solution is simply liquid.

This document is believed to qualify as prior art under 102(a) as evidence that the subject matter was known and used by others before the filing of the instant application. As indicated on pages 10-12, this presentation appears to have been presented to the RAC in a public meeting on 3/8/01.

Claims 1-12, 15, 18, 23-28, 30, 33, 36, 38-48, 51, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12), as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998). Clayman, G., Ref. C23 of the IDS filed 8/16/04 appears in this on-line publication at pages 10-11.

Recombinant DNA Advisory Committee (RAC) describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector (see pages 10-11 especially).

RAC does not mention papilloma virus infection of cells in the lesion, however, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment. Oda discloses that up to 90% of oral cancers have been reported to contain HPV DNA (p. 2003, col. 2), and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Consequently, one of skill in the art of oral cancer would have been aware that the treatment of Clayman described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells. With respect to the limitation that the composition be formulated as a douche solution (e.g. claims 18, 33, 54), a douche is simply a jet of liquid applied to a part of the body; so a douche solution is simply liquid.

Claims 1-14, 19-29, 34-50, and 55-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Nielsen et al., US 2001/0044420, as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998) with respect to claims 1-14, 19-29, 38-50, 55-60.

Nielsen describes the treatment of cancer in general, including cervical cancer and head and neck cancer, by a combination of p53 gene therapy and gemcitabine chemotherapy. The p53 gene can be delivered by non-viral lipid-based plasmid delivery or by delivery in a viral vector based on adenovirus, AAV, retrovirus, or vaccinia virus. The p53 coding sequence in the vector may be under control of a constitutive or tumor specific promoter. Nielsen discloses topical delivery of the vector to the location of a tumor, including to the surgical wound resulting from tumor resection. Pharmaceutical compositions comprising the vector include compositions for

transmucosal or transdermal delivery for treatment of tumors in the mouth, nasal mucosa, vagina and uterus are disclosed. Disclosed compositions include emulsions (i.e. cream, ointment or salve), aerosols, tablets, lozenges and suppositories. See entire document, especially paragraphs 0003-0006, 0009, 0013-0016, 0022, 0029, 0038, 0064, 0076, 0083, 0088-0093, and 0101-0104, and claims 1-10, 34-35.

Nielsen does not mention papilloma virus infection of cells in the lesion, however, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment where the cancer is head and neck or cervical cancer. Oda discloses that up to 90% of oral cancers have been reported to contain HPV DNA (p. 2003, col. 2), and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Consequently, one of skill in the art of oral cancer would have been aware that the treatment of Nielsen would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells when treating head and neck or cervical cancer in a substantial fraction of target patients. With respect to timed-release formulations, formulations such as creams, ointments, tablets, suppositories, etc. release their contents as the carriers break down over time, and so are timed-release.

Claims 1-15, 18-30, 33-51, 54-60 are rejected under 35 U.S.C. 102(b) as being anticipated by El-Deiry et al., WO 99/66946.

The instant specification (page 14, lines 5-10) states: "the term "p53" is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species". The

invention of El-Deiry relates to gene therapy with a transgene encoding p73, a homolog of p53 (El-Deiry, Abstract, page, 12, lines 32-33, and page 22, line 26, to page 23, line 23). Given the definition of "p53" in the instant specification, p73 is embraced by the term "p53" recited in the instant claims.

El-Deiry discloses the treatment of cells transformed by infection with a papilloma virus, such as HPV, particularly those in certain types of cancer involving papilloma virus infection, e.g. cervical cancer, esophageal squamous cell cancer, laryngeal papilloma, bronchio-alveolar carcinoma, penile carcinoma and bladder carcinoma. El-Deiry teaches methods of treating such cells *in vivo* by gene therapy with a vector that expresses p73, including by topical delivery. The vector may be a liposomal vector or a viral vector based on a retrovirus, adenovirus, and AAV. The p73 coding sequence is under control of a constitutive promoter or papilloma virus-regulated promoter. The pharmaceutical composition comprising the vector may also include a chemotherapeutic agent, and can be formulated as an aerosol for inhalation, in a lotion or suppository, in a liquid for oral delivery, or in a transdermal patch, and used such that the composition contacts the target cells. See entire document, especially page 1, lines 8-12 and 20-22; page 3, line 10, to page 5, line 7; pages 12-16; pages 20-23; page 24, line 33 to page 25, line 31. With respect to timed-release formulations, formulations such as creams, ointments, tablets, suppositories, etc. release their contents as the carriers break down over time, and so are timed-release.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 17, 31, 32, 52, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12), as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998), as applied to claims 1-12, 15, 18, 23-28, 30, 33, 36, 38-48, 51, and 54 above, or El-Deiry et al., WO 99/66946, as applied to claims 1-15, 18-30, 33-51, 54-60 above; and further in view of Zhang et al., WO 00/29024.

Recombinant DNA Advisory Committee (RAC), Oda et al., and Flaitz et al., and El-Deiry et al. are described above. RAC and El-Deiry et al. both describe liquid compositions for oral delivery of the vector, but neither describe inclusion of a flavorant in the composition.

However, Zhang et al. generally describes pharmaceutical compositions for gene therapy comprising an adenoviral vector, and teaches (pages 56-57) that compositions for oral delivery may include flavorants.

Therefore, it would have been obvious to one of ordinary skill in the gene therapy art at the time the instant invention was made to include a flavorant, such as peppermint or wintergreen oil, in a mouthwash containing the vector. The inclusion of flavorants in oral pharmaceutical compositions is routinely done to improve the palatability of the composition.

Request for Information

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

Document C95 cited on the PTO-1449 filed 8/16/04 has been determined to anticipate the claimed invention under 35 USC 102(a) as set forth above. The author of the presentation is not a named inventor of the instant application, and the "publication" date cited is more than one year before the earliest filing date to which priority is being claimed for the instant invention. The following information is requested in order to determine whether document C95 also qualifies as prior art under § 102(b), in light of *In re Klopfenstein*, 72 USPQ2d 1117 (Fed. Cir. 2004):

- the date, location, and audience (including their level of expertise) for each presentation of the PowerPoint presentation prior to 12/29/03;
- the length of time the information was displayed at each presentation and in what medium, e.g. whether the slides were displayed on a screen during a talk, whether hard copies, e.g. posters, of the slides were displayed and for how long, whether copies of the slides were passed out to the audience;
- whether there was an expectation that the displayed material might be copied, and the ease with which it could have been copied;
- whether any confidentiality restrictions were in place regarding the content of the presentation;

- whether the slide presentation or its contents were published or otherwise made publicly available in any format, be it printed or electronic, before 12/29/03, and if so, when, where and how; and
- whether the clinical trials proposed in the presentation had commenced prior to 12/29/03, and if so, on what date.

The PTO-1449 of 8/16/04 indicates that document C95 was sponsored by Introgen Therapeutics, which is the Assignee of the instant application. So, it is assumed that Assignee, at least, should be able to provide the information requested above.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER
Scott D. Priebe